REMARKS

Claims 1-2 and 11 have been cancelled. Claims 3, 6 and 7 have been amended. Claims 3-10 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Advisory Action

The Advisory Action sent March 8, 2007 stated that the Amendment of January 23, 2007 would not be entered because the amendment raised new issues that would require further consideration and/or search, raised the issue of new matter, and did not reduce or simplify the issues for appeal.

The continuation sheet to the Advisory action stated that the reference to "maintenance ...of a state of disease" was indefinite because the term "maintenance" was not defined in the specification and it was not clear what would be involved with a "state of disease". The Examiner further commented that "the specification does not contemplate monitoring blood vessel formation during a particular state or stage of a disease".

Responsive to these comments, the claims have been amended to "during the progression of a/the disease". It is respectfully submitted that this language is supported by the specification as discussed further below, and that one skilled in the art and even the ordinary person would understand what is meant by "progression of disease". Reconsideration is requested.

Rejection under 35 U.S.C. § 102(b) (Majka, et al. evidenced by Peichev, et al.)

Claims 3-6 are rejected under 35 U.S.C. § 102(b) as anticipated by Majka, et al. in view of Peichev, et al.

The Office Action states that the specification does not define "pathological angiogenesis", but that Example 2.1 discloses measuring pathological angiogenesis by determination of blood vessel formation evaluated by counting endothelial cells (Office Action, pages 3-4, bridging paragraph). The Office Action goes on to state that Majka, et al. monitor angiogenesis by monitoring of hematopoietic colonies after exposure of CD34+ cells to an anti-prominin-1 compound. Since CD34+ cells are endothelial as taught by Peichev, et al, the Examiner concludes that Majka, et al monitor pathological angiogenesis.

Majka, et al. relates to the use of prominin-1 as a marker for early human hematopoietic progenitor cells (page 59, Discussion, first paragraph). There is no teaching in Majka, et al. on measurement of pathological angiogenesis. Indeed, as indicated by the Examiner, such teaching is found in Applicants' specification at Example 2.1. The specification at Example 2.1 states that the "proliferative neovascular response is quantified by counting the number of new vessels (=tufts) and the number of endothelial cells extending from the internal limiting membrane of the retina into the vitreum on the stained sagittal cross-sections." (page 12, lines 16-19). Accordingly, the specification states specifically at least one way to measure pathological angiogenesis which is not taught by either of Majka, et al. or Peichev, et al.

Majka, et al. does not teach measurement of pathological angiogenesis or correlation of prominin-1 with pathological angiogenesis. Majka, et al. merely count hematopoietic CD34+ cells in which AC133 has been downregulated. Majka *et al.* do not disclose any role for prominin-1 in pathological angiogenesis, but instead only teach AC133 as a marker for early human haematopoietic progenitor cells (p. 59, 1st par. of Discussion). Moreover, Majka *et al.* did not detect any effect of AC133 downregulation on their haematopoietic, $CD34^+$ cells.

Majka, et al. identify various cell types which express prominin-1, including CD34+ progenitor cells which are associated with hematopoiesis. The goal of Majka, et al. is to identify stem cells, not monitor pathological angiogenesis and there is no teaching in Majka, et al. of how to measure pathological angiogenesis. Majka, et al. do not teach that the presence of prominin-1 correlates with pathological angiogenesis. Furthermore, while Majka, et al. teach detection of prominin-1 (by antibody or antisense oligodeoxynucleotide), Majka, et al. do not teach inhibiting expression of prominin-1 or monitoring of pathological angiogenesis.

In contrast, the present application for the first time demonstrates that pathological angiogenesis is diminished in the absence of AC133. The present application shows that AC133 is not required for embryonic development and postnatal physiological vascular development, since these processes are normal in the AC133 knock out mouse (present specification, page 11, lines 14-20). Taken together this substantiates that compounds identified in the screening assays according to the present claims would selectively impair pathological angiogenesis, while not interfering with normal, physiological angiogenesis.

Furthermore, claim 6 has been amended to replace "pathological angiogenesis" with "monitoring a reduction in the number of blood vessels during progression of a disease" based upon the definition given on page 7, lines 3-4 of the present specification. Dependent claims 3 and 7 have been amended accordingly. Support for this amendment is found both on page 7, lines 3-4 and in the examples. For instance, Example 2.1 on page 11 exemplifies the disease of ischemic retinopathy. Monitoring the blood vessels is taught at page 12, lines 16-19. See also, page 16, lines 11-13 which concludes that the data of the Examples "clearly indicate a role of AC 133 in pathological vasculogenesis and/or angiogenesis and implicate the use of inhibitors of PROM-1 in therapeutic strategies to inhibit blood vessel formation in various pathological disorders.". Applicants respectfully submit that the claims as amended are supported and enabled by the present specification.

Neither Majka, et al. nor Peichev, et al. teach monitoring pathological angiogenesis by monitoring formation and growth of blood vessels in association with a disease state. Accordingly, the presently claimed invention is clearly distinguished from the teachings of Majka, et al. and Peichev, et al, either separately or taken together.

Furthermore, Majka, et al. do not enumerate endothelial cells. More specifically, Majka *et al.* downregulate prominin-1 in all $CD34^+$ cells (p. 58, col. 1, last par. of Majka *et al.*). However, Peichev *et al.* teach that only a minute fraction of $CD34^+$ cells – those co-expressing VEGFR-2, being about 1-2% (abstract of Peichev) – may represent circulating endothelial cells. Therefore, by assaying all $CD34^+$ cells, Majka *et al.* enumerate an overwhelming majority of non-endothelial, haematopoietic cells and do not specifically monitor the effect of prominin-1 downregulation in endothelial cells. This is also corroborated by the fact that Majka *et al.* study the effect of prominin-1 downregulation in $CD34^+$ cells differentiated into various hematopoietic lineages (CFU-Mix, BFU-E, CFU-GM, CFU-Meg; p. 58, col. 2, pars. 1 and 2 of Majka *et al.*) but never on $CD34^+$ cells differentiated into endothelial cells. Consequently, Majka *et al.* do not teach monitoring the effect of prominin-1 antagonists on angiogenesis, let alone on pathological angiogenesis.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 3-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Peichev, et al. and Majka, et al. in view of Babinet, et al. and further in view of Murphy, et al.

Regarding claims 3-6, the arguments presented above are reiterated here. It is respectfully submitted that the Majka, et al. and Peichev, et al., taken separately or together, fail to teach or suggest the present claim limitations.

Claims 7-10 depend from claim 6 and are also believed to be patentable, at least because they include all of the limitations of claim 6.

Babinet, et al. and Murphy, et al are relied upon to show the use of knockout mouse models which pertains to claims 7-10. However, neither Babinet, et al nor Murphy, et al correct the defects of Majka, et al. and Peichev, et al. discussed above.

Claims 7-10 are additionally patentable for the following reasons. Claim 7 has been amended to recite specifically "measuring formation and growth of blood vessels during the progression of the disease in the knock-out model compared to formation and growth of blood vessels during the progression of the disease in a corresponding normal subject" based upon the definition given on page 7, lines 3-4 of the present specification, and consistent with the amendment to claim 6. Further support for this amendment is found at page 12, lines 16-19 as discussed above.

None of the cited references teach administration of prominin-1 antagonists in a model of pathological angiogenesis. Moreover, because the role of AC133 *as such* in pathological angiogenesis is not disclosed and not suggested in any of the cited references, there was no motivation for one of ordinary skill in the art to administer such molecules in a model of pathological angiogenesis at the time of the claimed invention.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the

application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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